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October 1959

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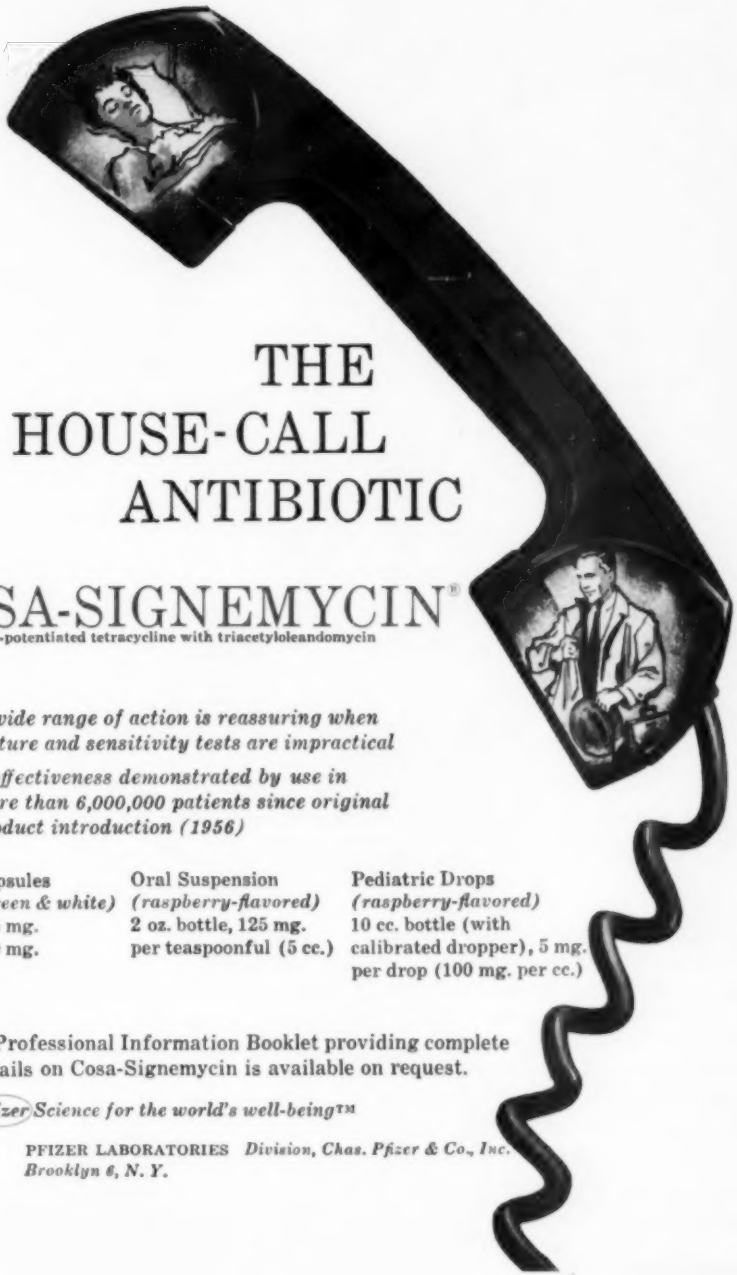

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1. Koessler, H. W.: Arch. Ped. 74:47 (Feb.) 1957.
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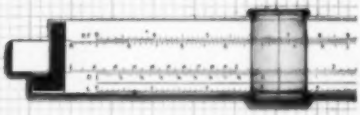

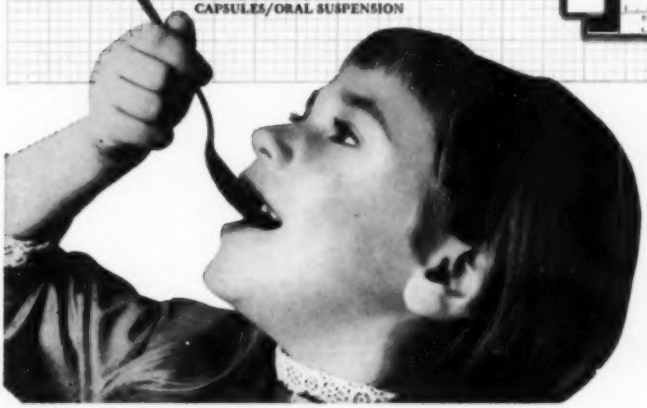

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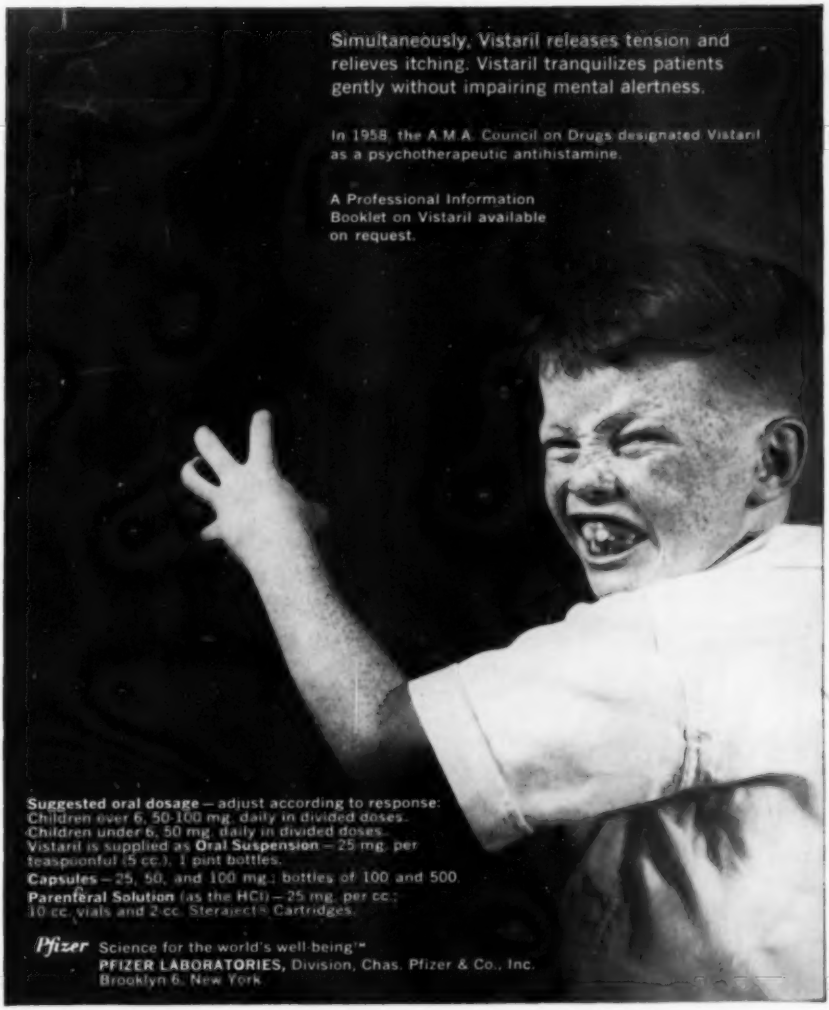
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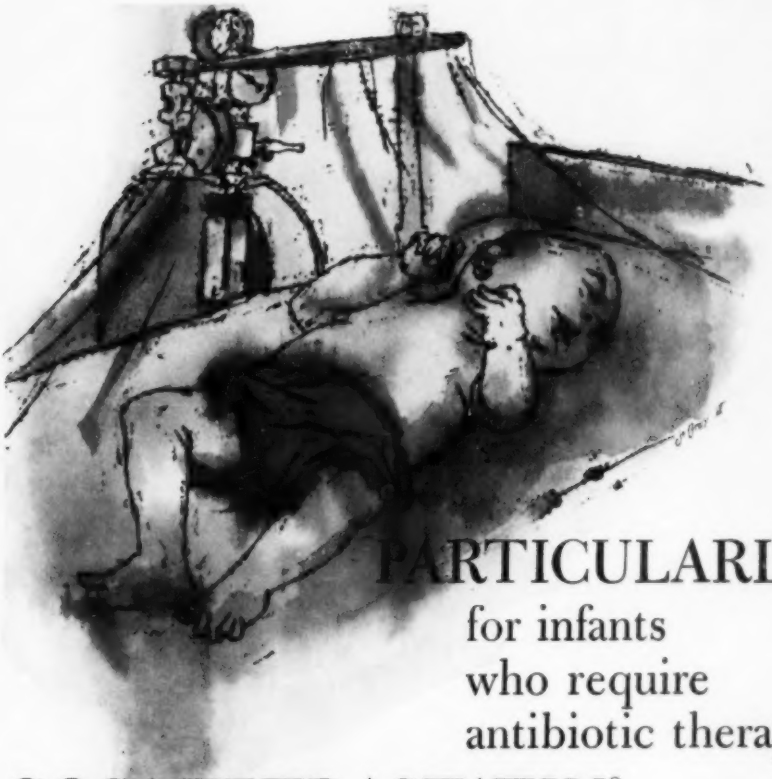

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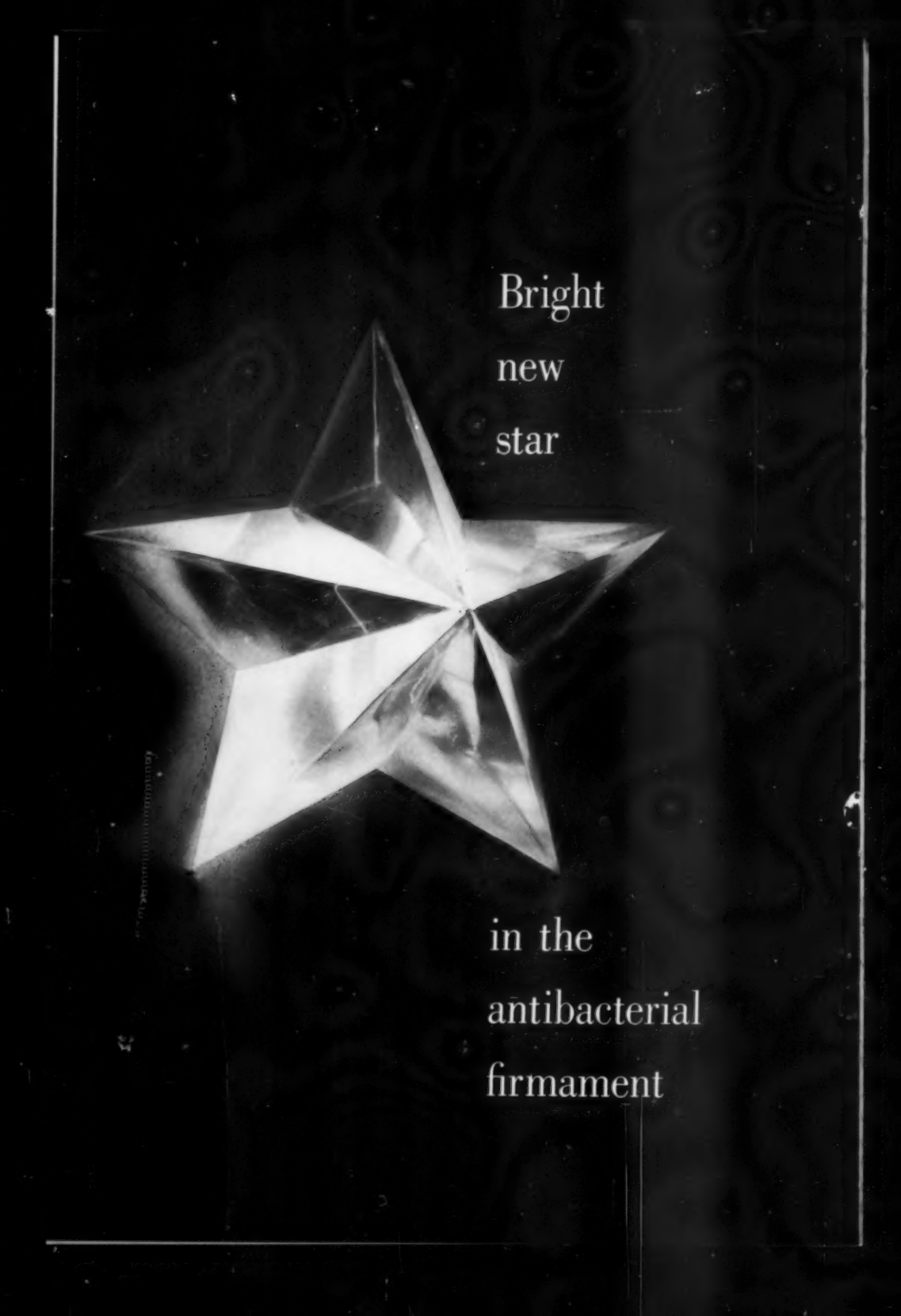
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1. Litchfield, H. R.: Archives Pediatrics 74:463, 1957

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ARCHIVES of PEDIATRICS

October 1959
Vol. 76 No. 10

PERTUSSIS ENCEPHALOPATHY

H. ZELLWEGER, M.D.*

Lebanon

Neurological complications of pertussis concern the brain almost exclusively. Involvement of the spinal cord, and peripheral nerves is extremely rare, if it occurs at all. There are a very few reports of meningitis due to H. pertussis (Schoenberg),[1] yet other authors are somewhat doubtful, and prefer to think of a super-infection with H. influenza[2]. The incidence of so called pertussis encephalopathy is difficult to establish. The data recorded in the literature vary from 1.5% to 14%[7] of all cases of whooping cough admitted to the respective centers. The true incidence is probably considerably less, since many cases with uncomplicated pertussis are neither hospitalized nor reported.

ONSET

In eight per cent of 148 cases collected from the literature,[3,4,5,6,7] the neurological complication began in the first weeks of the primary disease, in 76% within the second and fourth week, and in 8% during the fifth week. This is a longer time interval than that seen in post-infectious encephalitis, which coincides to some extent with the convulsive stage of pertussis (Table 1).

The encephalopathy is a complication of the very young; cases over 10 years are rare exceptions—if occurring at all.[1,3,4,5,6,7]

The susceptibility of girls appears to be higher than that of boys, 59% of 88 cases compiled by Miller and Stanton[2] were girls, 41% boys.

As to the clinical course, two forms can be distinguished. The first form begins suddenly with convulsions, followed by a state of unconsciousness or coma with varying neurological symptoms. In

* Chairman, Pediatric Department, American University Hospital, Beirut, Lebanon.

the second form the onset is more insidious; the temperature rises within a few days to a high fever, even to hyperpyrexia, the patients become progressively somnolent, comatose and even unconscious. In this form convulsions, as well as other neurological symptoms, as pareses, hemiplegia, paraplegia, motor aphasia, and decerebrate rigidity may appear. Exceptionally pertussis encephalopathy imitates an acrodynia-like picture of a confused state.[7] The blood reveals a lymphocytic leukocytosis, which is higher than in uncomplicated pertussis and reaches 30,000-50,000 WBL per cumm. The spinal fluid is normal, or reveals a mild to moderate pleocytosis, with an increase in the proteins. Habel[4] found in 6 of 23 cases a cell count above 10 per cmm; in 5 cases the cell count was between 10 and 100, and in one case more than 100 cells. In half of 21 cases observed by Zellweger and Steinegger,[7] a mild pleocytosis of not more than 45 cells was found; in 17 of them, the spinal fluid proteins were between 36 and 101 mg%. The case reported by Schoenberg,[1] Fanconi, Zellweger, and Botsztejn[8] with more than 2000 mg% proteins, is not a simple case of whooping cough encephalopathy, since it occurred in a child with a previously damaged brain (congenital hydrocephalus), suffering a simultaneously from whooping cough and aphthous stomatitis.

TABLE 1

Onset of Pertussis-encephalopathy

Week of pertussis	No. of cases of encephalopaths		
1	13	8%	
2	38		
3	44	76%	84%
4	30		
5	16	8%	
6	6		
7	1		
Total	148		

The duration of the encephalopathy varies between several days and several weeks. A few cases have been observed where a state of decerebrate rigidity persisted for nearly two months. The mortality is highest in the first few days after onset of the neurological

complication; about one-third, or according to some authors as high as 80% of the cases die. The mortality rate within the first week of the encephalopathy is higher than in later weeks. However the longer the disease lasts the greater is the chance of permanent brain damage. Sequelae consist of mental retardation of varying severity, paralyses and palsies, focal or generalized convulsions, ataxias, amaurosis, and changes of personality and behaviour. In general one third of the patients recover without sequelae, and one third may be afflicted with any of the above mentioned sequelae.

TABLE 2

Age Incidence of Pertussis-encephalopathy

Age in years	Number of cases
0-1	77
1-2	45
over 2	53

The pathogenesis of pertussis encephalopathy has been a matter of considerable discussion for many years. Many different mechanisms have been suggested as being the cause of the neurological complications (Table 3). It has been believed that air embolism, or massive hemorrhages were the etiological factors; indeed in very occasional cases gross hemorrhages were found. In a number of earlier publications tetany was mentioned. In the children's hospital in Zürich signs of tetany as evidenced by Erb's signs, hypocalcemia etc. were found in about one third of over 40 cases[1,7]. The incidence of rickets and tetany as manifestations of simple vitamin D deficiency, has decreased so much in recent years, that pertussis as a precipitating factor of tetany has become exceptionally rare.

TABLE 3

Earlier Concepts of Pathogenesis of Pertussis-Encephalopathy

I Vascular
- a. Hemorrhages
  - 1. Mechanical
  - 2. Toxins
- b. Angiospasms, Ischemia
- c. Anoxemia
- d. Edema, congestion

II Inflammatory
- a. Viral
- b. Bacterial

III Air Emboli

IV Tetany

More recently toxemia and anoxemia have been widely accepted as probable mechanisms involved in the pathogenesis of whooping cough encephalopathy. Toxis effects and anoxemia due to circulatory stasis, can account for most of the anatomical findings

e.g. edema, eosinophilic degeneration of ganglion cells, and purpura cerebri[3,10,8]. These changes are not specific for pertussis encephalopathy, since they, excluding purpura, are found as well after convulsions and other processes associated with brain anoxia. Pertussis toxins injected intracerebrally or intrathecally into guinea pigs produced convulsions[12]. In the majority of the cases of pertussis encephalopathy no signs of inflammation were found. Therefore the term encephalosis or encephalopathy has been accepted as being more appropriate than the previously used term encephalitis. However, in a few cases true encephalitic changes were found. Askin and Zimmermann,[13] for instance, reported a case with scattered mononuclear and polynuclear infiltrates, which were not related to the vessels. This case is not unanimously accepted as a pertussis complication, some authors considering it as a superimposed viral infection. Woolf and Caplin[14] described the case of a 3 year old girl, who died of respiratory failure soon after the onset of an epileptic state, which occurred in the seventh week of pertussis. A pleocytosis of 80 cells was found in the spinal fluid. The autopsy revealed ganglion cell degeneration in the cortex, as found in other cases of pertussis encephalopathy, yet in addition the brain presented the picture of meningoencephalitis with lymphocytic infiltrates in the meninges and perivascular cuffs of lymphocytes in the white matter. Dolgopol[3] found in one of her cases, foci of demyelination in the white matter associated with eosinophilic degeneration in the cortex. Moeller also reported the case of a 2½ years old girl, who during pertussis went into a state of respiratory and circulatory insufficiency and died in shock. The autopsy of the brain revealed perivascular necroses, perivascular cuffs of leucocytes, microglia, plasma cells and extensive disseminated demyelinazation as seen in some postinfectious encephalitides (perivenous syndrome).

CONCLUSIONS

In conclusion it can be said, that various antomical changes have been found in the brain autopsy of patients, whose pertussis was complicated by neurological manifestations. (Table IV). Encephalitic changes and perivenous syndrome in pertussis are exceptional. yet do occur; more frequent are signs of toxic—vascular or of ischemic encephalopathy. It is most probable that different pathogenetic mechanisms are responsible for the different anatomical pictures. The situation is therefore somewhat similar to some of

the post- and parainfectious encephalitides, where different pathogenetic mechanisms lead to an identical clinical symptomatology yet with different pathological findings.

TABLE 4

Some pathological Fndings in Pertussis-encephalopathy (Dolgopol[3])

Total	15 cases
Edema	14 "
Eosinophilic degeneration	13 "
Multiple Petechiae	12 "
Lymphocytic plugs in veins and capillaries	11 "
Subarachnoid hemorrhage (small)	7 "
Meningitis	1 "
Demyelination	1 "

The question arises as to whether or not some children are more susceptible to pertussis encephalopathy than others. An answer to this may be obtained from the analysis of the family history, and of the personal history before the beginning of the pertussis. In 20 of 23 families in which a case of pertussis encephalopathy had occurred, there was an unusual incidence of neurological conditions in other members of the family (Table 5).

TABLE 5

Neurological and Nervous Conditions in 23 Families, Where A Pertussis-encephalopathy Occurred

	No. of Families
Epilepsy	2
Psychoses	7
Mental retardation	2
Migraine; tendency to syncope	14
Excessive nervousness	11
Alcoholism	2

This may indicate a familial susceptibility of the central nervous system, but certainly a greater number of observations, and a control study in uncomplicated pertussis, or in families of normal children is required before definite conclusions can be reached.

Since pertussis encephalopathy occurs usually at a very young age, it is difficult to assess the previous history for neurological and related conditions. We reported earlier[7] the case of a boy, whose pertussis encephalopathy (at 4½ years) was preceded by hypocalcemic (non rachitic) convulsions at the age of 3 months, with signs of anorexia and constitutional fever. The history of a girl with pertussis encephalopathy at the age of nearly 7 years revealed a history of head nodding, nightmares, and other signs of emotional instability. Further studies in this direction are required before any conclusions can be drawn.

The therapy is symptomatic. Antibiotics, in particular Chloromycetin or Rovamycine* are certainly indicated to overcome the basic disease, and prevent further production of toxins. Symptomatic treatment of the paroxysmal cough may help to prevent anoxemia. The effect of steroid therapy on the encephalopathy has so far not been sufficiently evaluated.

SUMMARY

Whooping cough encephalopathy is found most frequently in infants and younger children. It is more common in girls than boys, and occurs mainly between the second and fifth week of pertussis.

The clinical course, etiology and prognosis are discussed. One third of the cases recover without sequelae, one third with sequelae, and one third is incurable.

Whooping cough encephalopathy is due to the effect of pertussis toxin and anoxemia on the brain. It is not a true encephalitis, though in exceptional cases encephalitic changes have been found. It is suggested that a careful analysis of family and personal history of cases with encephalopathy may disclose possible constitutional factors favoring the occurrence of neurological complications in pertussis.

*(Spiramcyine)

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HEMOLYTIC DISEASE OF THE NEWBORN

A Survey of 91 Cases

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This paper summarizes our experience with hemolytic disease of the newborn at the Maimonides Hospital of Brooklyn, during a period covering January 1, 1956 to January 1, 1958. In general, our results parallel those of previous studies. However, on detailed analysis, certain findings have emerged which we feel are sufficiently significant to warrant further attention.

MATERIAL

The patients studied were all those admitted to the obstetric service, including both private and ward patients. In the two year period a total of 7202 women were delivered of 91 diagnosed erythroblastotic babies, including one set of twins. Unfortunately, our records are incomplete for the major blood group determinations of all the mothers during the first fourteen months of this survey. The distribution of blood types for the latter ten months, which include 2945 cases, is given in Table 1. The Rh groupings are complete for the entire year of 1957 (Table 2). The higher incidence of Rh positive individuals can be explained by a predominantly Jewish population in this area plus a liberal sprinkling of Puerto Ricans. Both of these groups are known to have a higher percentage of Rh positive reactors.[1,2]

PHYSIOLOGICAL JAUNDICE

We originally had the impression that many cases of mild Erythroblastosis were being classified as "Physiological Jaundice." We therefore undertook to analyze all such instances by a study of blood groups. In 1957, there was a total of 264 cases diagnosed as "Physiological Jaundice." Of these, all mothers were recorded as to Rh typing; only 169 were identified as to major grouping. The breakdown, (Table 3), indicates there is no significant increase in either Group O or Rh negative women in the total group of physi-

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TABLE 1

Distribution of 2945 Mothers by Blood Group

Group	*Number*	*%*
A	1156	- 39
B	468	- 16
AB	161	- 6
O	1160	- 39

TABLE 2

Distribution of 3642 Mothers by Rh Type

Group	*Number*	*%*
Rh Pos.	3237	- 89
Rh Neg.	405	- 11

ological jaundice cases. Although this does not confirm our first supposition, we feel that this line of investigation could be pursued profitably in a larger series of cases.

TABLE 3

Blood Group Distribution of 169 Women Whose Babies Had Physiological Jaundice

	% Jaundiced		*Overall %* (Table 1)
Group	*Number*	*%*	*%*
O	71	42	39
A	58	34	39
B	32	19	16
AB	8	5	6
Rh Neg.	28	10.6	11
Rh Pos.	236	89.4	89

MATERNAL OBSTETRICAL HISTORY

Eighty-four out of ninety mothers who gave birth to erythroblastotic babies had a clearly recorded history. There were fifteen primiparae and sixty-nine multiparae. The distribution by parity is given in Table 4. The mothers with a positive history of previous erythroblastotic children are detailed in Table 5. It is seen that 9 percent of the group had a positive history. Seven out of the eight babies required at least one exchange transfusion. This confirms the previous observation that the maternal history is of the utmost prognostic importance.

TABLE 4

Parity of 84 Women with Erythroblastotic Babies

Previous Pregnancies	*N. of Cases*
0	15
1	35
2	24
3	2
4	5
5	2
6	1

TABLE 5

Relation of Maternal History to Frequency of Exchange Transfusion in Offspring
8 out of 90 Cases Had a Positive History—9%

Patient	*Bl. Type*	*Parity*	*Previous Babies*	*Treatment*
M.	A neg.	2	1—Died; 1—Ery.#—Ex.°	2 Ex.
D.	A neg.	1	Prem. with Cong. Anom.	1 Ex.
G.	O neg.	5	4—Normal; 1—Ery.—Ex.	1 Ex.
V.	O neg.	4	2—Normal; 2—Ery.—Ex.	1 Ex.
E.	O pos.	2	1—Normal; 1—Ery.—Ex.	0 Ex.
S.	O pos.	1	1—Ery.—0 Ex.	1 Ex.
W.	O pos.	1	1—Ery.—Ex.	1 Ex.
A.	O pos.	1	1—Ery.—Stillbirth	1 Ex.

Erythroblastosis
° Exchange Transfusion

TYPE OF INCOMPATIBILITY

All the incompatibilities identified in this series of 91 erythroblastotic infants were either of the O-AB or Rh type except for one instance of hr' (c) sensitivity. The incidence of these combinations is given in Table 6. The major blood group of four Rh positive babies was not recorded. It is seen that there is a striking preponderance of O-A incompatibilities in this series, comprising 75% of all O-AB cases. This contrasts with a 39.2% incidence of group A mothers in the overall series. On the other hand, there was an incidence of 12.5% of O-B incompatibility as against an incidence of 16% of group B mothers. It would appear that the A factor is a more potent sensitizing agent than the B factor, when present in a group O mother.

ONSET OF CLINICAL JAUNDICE

When the onset of clinical jaundice in the baby is correlated with the type of treatment, it confirms the previously reported observation[3] that the earlier the onset of jaundice the more severe

the hemolytic process. In Table 7 the number of babies requiring exchange transfusion is related to the first appearance of jaundice.

TABLE 6

MOTHER

		A+	B+	AB+	O+	A—	B—	AB—	O—
	O—								1
	AB—						2		
B	B—				1				
A	A—				2	1			1
B	O+				3	3	1		5
Y	AB+		1		1		1		1
	B+				5		3		1
	A+	2			33	11	2		5
	Und.°				4				1

° Undetermined

TABLE 7

Time of Onset of Jaundice Related to Transfusion Therapy

Day	*No. of Cases*	*1 Ex.#*	*2 Ex.*	*1 S.° & 1 Ex.*	*1 S.*	*% Ex.*
Birth	1			1		100
1	24	11	2	4		71
2	39	17	2	5	1	62
3	18	4		1	1	28
4	4			1	1	25

Exchange Transfusion
° Simple Transfusion

CORD BILIRUBIN

In Table 8 the level of cord bilirubin is related to the necessity for exchange transfusion. It is seen that when the cord bilirubin was above 4 mg. percent, exchange transfusion was almost invariably necessary—only one baby out of seventeen did not need to be transfused. Between levels of two to four mg. percent, about one out of three babies did not require exchange transfusion.

SERUM BILIRUBIN

Serum bilirubin determinations were recorded on the chart in 75 out of 91 cases. The maximum levels reached are divided into three groups:

1. Under 10 mg.%—20 cases
2. 10—20 mg.% —36 cases
3. Over 20 mg.% —19 cases

In group 1, 60 percent were transfused; in group 2, 70 percent; in group 3, 74 percent.

It is interesting to note that five babies with serum bilirubins between 20 mg. percent and 22.6 mg. percent did not receive exchange transfusions. Four of these children have been followed past the age of one year. One of them has had recurrent convulsive seizures.

Three instances were recorded above 30 mg. percent. The first was a case of an O Rh positive mother with an A Rh positive baby who had a negative Coombs test and an initial hemoglobin of 10.3 Gm. percent. The serum bilirubin attained a level of 34 mg. percent. One exchange trtnasfusion was performed with good results. The second case occurred in an O Rh positive baby from an A Rh negative mother; the Coombs test on the baby's red cells was strongly positive. Two exchange transfusions were done with a favorable outcome. The third case represents the only case of kernicterus and fatality in this series. This was an instance of c (hr') incompatibility in an A Rh positive baby (Genotype A_1, M_1, Rh_1, Rh_2) with an A Rh positive mother (Genotype A_1, MN, Rh_1, Rh_1). Great difficulty was experienced in finding compatible blood for this baby, resulting in unavoidable delay in the exchange transfusion. The bilirubin reached a level of 30.6 mg. perecnt. The baby died on the fifth day. Autopsy showed severe Erythroblastosis and Kernicterus.

TABLE 8

Cord Bilirubin Related to Transfusion Therapy

Bilirubin in mg.%	*No. of Cases*	*None*	*1 Ex.*°	*2 Ex.*	*% Ex.*
0-2	14	7	4	3	50
2-3	18	7	8	3	61
3-4	16	5	10	1	69
4-5	10	1	6	3	90
5-6	6	0	3	3	100
6-8	1			1	100

° Exchange Transfusion

° All references to Bilirubin determinations are to indirect Bilirubin.

MATERNAL SENSITIZATION STUDIES

Out of 440 Rh negative mothers delivered in 1957, 5.2 percent, or 23 gave birth to erythroblastotic babies. This figure agrees well with previous reports[4]. Out of 1160 Type O mothers, 2.5 percent or 29 produced erythroblastotic offspring. These figures include ten Type O Rh negative mothers who are therefore counted in both groups for statistical purposes. Five of these ten, however, had a negative Coombs reaction on the cord blood, associated with a clinically mild erythroblastosis in the baby. These may be considered examples of O-AB incompatibility. The other five all had positive direct Coombs tests on the cord blood, as well as demonstrable anti-Rh_0 antibodies in the mother. These were also more severe than the preceding five and must be considered cases of Rh incompatibility.

In 1957, there were 34 Rh negative mothers who developed demonstrable anti-Rh_0 antibodies. These produced 18 erythroblastotic babies and one macerated fetus; the remaining 15 mothers had normal offspring. Of the fifteen normal babies, three were Rh negative, and eight were Rh positive; the remaining four were not recorded due to varying circumstances. Thus there were at least eight Rh_0 positive babies without hemolytic disease who were born to sensitized mothers.

The antibody titers were determined by saline, trypsin, and Coombs techniques. The highest values attained by any of these methods, usually the Coombs titer, are listed below (Table 9). It is seen that the erythroblastotic babies tend to occur in the mothers with the higher titers. However, it is obvious that there is no strict relationship as has been brought out before.[5]

TABLE 9

Maternal Antibody Titer Related to Incidence of Erythroblastosis

Titer	*Normal*	*Erythroblastosis*
1		2
2	2	1
4	7	3
8	3	2
16	2	1
32	1	1
64		3
256	1	2
320		1
1024		1

TRANSFUSION THERAPY

The decision to transfuse a baby was governed by a careful synthesis of all the various maternal, clinical and hematological factors in each individual case. As previously indicated, a bad maternal neonatal history and/or a high antibody titer were important considerations favoring early exchange transfusions. The time of onset of jaundice and the rapidity of its progress, the presence of hepato-splenomegaly, edema or hemorrhages, and the general condition of the baby were other critical evaluations. An initial hemoglobin of less than 14.5 Gm., a positive Coombs test, a cord bilirubin above 4.0 mg. percent and/or a rapidly rising serum bilirubin level also indicated transfusion therapy.

Using these criteria, 53 out of 91 infants had exchange transfusions performed. Of these, 34 (64 percent) had a single exchange; four (8 percent) had two exchanges; 12 (22 percent) had one exchange plus a simple transfusion; and 3 (6 percent) had a simple transfusion of packed cells.

RESULTS

Out of ninety-one erythroblastotic babies in two years, there was one mortality. This was the child with c (hr^1) incompatibility, who died on the fiifth day as a result of kernicterus. There were no other cases of kernicterus in this entire group. All exchange transfusions were done through the umbilical vein by Diamond's method.[5] There was no mortality from the procedure itself.

DISCUSSION

Of a total of ninety-one erythroblastotic babies, forty-one were caused by O-AB incompatibility, seven out of every eight of these being due to O-A disease. Almost 50 percent of this group were severe enough to require exchange transfusion by the usual criteria. It would seem that the usual concept of O-AB disease being a relatively benign process must be reevaluated.

Another observation worth noting has been our experience that when the cord bilirubin is above 4 mg. percent, about 94 percent of the babies had to be treated by exchange transfusion (16 out of 17). It is usually stated that a cord bilirubin above 5 mg. percent makes exchange transfusion almost mandatory. Further experience in larger groups of cases may lower this figure to 4 mg. percent.

Five infants whose serum bilirubin exceeded values of 20 mg. percent were not treated by exchange transfusion, according to the evaluation of the attending physicians at the time. All five left the hospital in good condition. One was lost to follow-up. Of the remaining four, one child, now three years old, has had recurrent seizures since the age of six months. The other three are normal.

SUMMARY

1. In a two year period, 7202 women were delivered of ninety-one diagnosed erythroblastotic babies.

2. There were 264 cases diagnosed as physiological jaundice. No significant increased incidence of Group O or Rh negative mothers was observed in this group.

3. A history of erythroblastosis in previous offspring is most important in determining severity and prognosis.

4. The A blood group factor appears to be a more potent sensitizing agent in a group O mother than the B factor.

5. A cord bilirubin of 4 mg. percent or above in this series was followed by an exchange transfusion in 94% of cases.

6. Fifty-three out of ninety-one affected infants received exchange transfusion. There was one fatality due to kernicterus.

7. Almost 50 percent of forty-one cases of O-AB hemolytic disease required exchange transfusion.

8. Only a rough correlation existed between the height of the maternal antibody titer and the severity of the hemolytic disease in the baby.

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STUDIES ON BLOOD AMINO ACID NITROGEN IN NORMAL EGYPTIAN INFANTS AND CHILDREN AND IN CASES OF NUTRITIONAL EDEMA

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The subject of amino-acids is of special interest to pediatricians because of the fact that protein requirements in infancy and childhood are comparatively much higher than at other age periods and also because there are many clinical conditions occurring at this age which are related to congenital anomalies in amino-acid metabolism.

Normally amino acids are produced in the intestines by the enzymatic breakdown of dietary proteins. They are then absorbed without further change into the blood stream, to circulate throughout the body as a result of which circulation an equilibrium is established for each amino-acid between the blood and the tissues. A certain proportion of them is consumed in each tissue to accommodate for growth, and also to replace the waste caused by wear and tear. Another part enters into the formation of many essential biological constituents as enzymes, hormones, bile salts, creatine, purines etc. . . ., While the remainder, probably the major part, normally undergoes deamination in the liver, the nitrogen radicle being converted into urea, which is excreted by the kidneys, and the non-nitrogenous part being carried to the tissues, where it serves as a ready source of energy. Their ultimate metabolic fate is closely related to the metabolism of carbohydrates and fats.

There is always a lower level of amino acids in the hepatic vein than elsewhere in the body, indicating that the liver is constantly removing amino acids from the blood.

During starvation, the venous return from the tissues is found to have an amino-acid content higher than that of arterial blood. This denotes that in starvation, the muscles and other resting tissues undergo a catabolic process, yielding amino-acids to the blood, to be available for more vital tissues, where continued work is essential for maintenance of life.

The importance of amino-acids in the body is indicated by the fact that they are present in the tissues as well as in the blood, even after complete starvation for some days. They, thus, should be considered as intermediate steps, not only in the synthesis, but also in the breaking down of body proteins and should, therefore, be considered as protein currency of the body, just as glucose is the carbohydrate currency.

The aim of the present work is to establish the normal levels of total amino acid nitrogen in the blood among Egyptian infants and

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children, and to see how far these levels are affected in cases of nutritional edema occurring during this age period.

EXPERIMENTAL WORK

Seventy cases were collected from apparently normal infants and children coming into Abbassia Children Hospital accompanied by their relatives. Of these, 24 were between 1 and 12 months, 25 were between 1 and 4 years and the remaining 21 were between 4 and 10 years. Clinically, they were found to be normal in every respect.

Regarding nutritional oedema, 23 cases were collected and studied. Two of them were below one year, while the rest between 1 and 3 years. They were all suffering from marked generalised oedema.

Sex, age and weight, were recorded for both the normal and diseased cases. Then 3 c.c. of fasting citrated blood were taken from each case for the estimation of total blood amino acid nitrogen.

The method of estimation used was that introduced by Danielson[1] and modified by Sahyun[2]. It is based on estimating the color developed by reaction between amino acids and β-naphthoquinone-4-sulfonic acid, in alkaline solution. This color is colorimetrically compared with that produced by standard amino acid solutions similarly treated.

Besides the amino acid nitrogen determination in cases of nutritional oedema, a liver puncture biopsy was examined and also an estimation of the total blood proteins and albumin fraction were carried out. This was done to look for possible relationship between the amino-acid level, the blood proteins and the liver condition among the cases of this group. For the same reason, a follow up of 5 cases was carried out by serial liver puncture biopsies and repeated blood examinations.

RESULTS

The data obtained in the normal and in the diseased cases studied, are given in the following tables.

DISCUSSION

I—Concerning Normal Cases:

The figures obtained for normal infants, showed an amino acid nitrogen content of whole blood varying between 5.1 and 8.9 with an average of 7.05 mg%. According to Snyderman[3] up to 1958, there had not yet been any investigation for the amino acid content in this group. The present figures could thus fill this gap.

Table I

Shows the amino acid nitrogen content of whole blood in normal cases

	Cases between 1&12 months				Cases between 1&4 years				Cases above 4 years			
No	Sex	Age in ms.	wt. in Kg.	Blood A.A. nitrogen mg %	Sex	Age ms-yrs	wt. in Kg.	Blood A.A nitrogen mg %	Sex	Age ms-yrs	wt. in Kg.	Blood A.A. nitrogen mg%
1	M	1⅓	4.0	7.6	F	6- 3	14.0	6.70	F	-- 5	18.50	6.50
2	M	2	4¾	7.1	F	10- 1	12.0	8.95	F	6- 4	15.00	5.40
3	F	2½	5.0	7.3	F	5- 2	13.0	6.60	M	1- 5	17.00	6.70
4	M	3	5½	7.6	M	6- 1	9.2	7.80	F	3- 5	17.30	8.80
5	F	3	5¾	8.4	F	6- 1	10.5	6.70	M	-- 5	17.80	8.70
6	F	3	5½	7.5	M	2- 1	9.5	5.20	M	-- 6	19.20	8.00
7	F	4½	6½	6.6	M	6- 2	12.0	8.20	M	6- 5	17.10	8.10
8	M	5	6¾	7.0	M	10- 1	11.3	5.40	F	8- 5	18.20	7.90
9	F	6	7	7.2	F	6- 1	10.3	5.30	M	1- 6	18.50	8.60
10	F	7	7½	8.8	M	10- 1	11.5	8.90	F	4- 5	19.00	7.40
11	M	7	7¾	8.5	F	-- 4	16.7	8.50	F	-- 5	18.50	7.60
12	M	8	8	8.7	F	-- 3	14.3	7.60	F	7- 5	17.90	7.80
13	M	8	7½	6.9	M	-- 4	16.1	7.60	M	-- 5	16.00	9.00
14	F	9	8	8.5	F	-- 3	14.1	7.00	F	2- 8	23.50	9.30
15	M	10	9	7.5	M	1- 1	9.2	7.60	M	6- 6	20.20	8.90
16	M	10	8½	7.2	M	8- 1	10.9	7.50	M	--10	29.00	7.80
17	M	10	8¼	7.1	M	8- 2	11.5	8.00	F	-- 8	22.80	6.40
18	F	11	9	7.5	M	-- 2	11.1	7.20	F	--10	26.00	6.30
19	F	11	9¼	5.2	M	-- 3	13.2	9.20	M	-- 9	25.50	7.60
20	M	11	9½	8.0	F	1- 1	9.5	9.40	F	-- 7	22.30	6.20
21	F	12	9	5.1	F	9- 1	10.4	8.80	M	-- 8	24.10	7.70
22	F	12	9	7.1	F	3- 3	14.0	8.40				
23	F	12	10	8.1	F	-- 2	11.3	8.20				
24	M	12	9¼	8.9	M	2- 1	10.0	7.90				
25					M	-- 2	11.5	7.19				
Average				7.1	Average			7.62	Average			7.65

The levels obtained among the two groups of normal children showed no significant variation as between 1 and 4 years, they varied from 5.2 mg% to 9.2 mg% with an average of 7.62 mg%, while in the cases between 4 and 10 years they varied from 5.4 mg% to 9.3 mg% with an average of 7.65 mg%.

It is obvious that the levels obtained for infants do not vary significantly from those obtained for children.

Very little work has been done on amino acid nitrogen content in childhood. However, Snyderman[3] had stated that the content is in the same range as in adults. Consequently, for comparison, one can use the figures given by other authors for both children and adults. Again, most of the works done on adults were on the plasma content. However, Hawk,[4] in his text book of Practical Physiological Chemistry, states that the amino acid nitrogen con-

Table II

Shows the levels of amino acid nitrogen content in case of nutritional oedema

Sr. Nº	Sex	Age ms-ys.	Weight Kg.	Total blood proteins gm %	Album. fraction gm %	Liver conditions as revealed by by puncture biopsy	-amino nitrogen in whole blood mg %
1	M	6- 2	12.500	4.1	1.31	++++	12.0
2	M	-- 2	8.350	4.6	2.20	++	9.7
3	M	-- 2	9.530	4.2	2.30	++	9.4
4	M	6- 2	8.820	4.9	2.20	++	9.9
5	F	10- 2	12.400	5.5	2.20	++	9.0
6	F	-- 3	10.000	3.2	1.40	++++	13.0
7	M	3- 1	8.250	4.9	2.08	++	8.7
8	F	8- 1	8.600	4.4	2.20	+++	10.0
9	F	-- 2	10.250	4.7	1.40	++++	9.9
10	F	3- 2	10.600	4.2	1.35	++++	13.2
11	M	-- 2	8.400	4.6	1.32	++++	12.1
12	M	--- 2	8.500	4.2	1.99	+++	11.1
13	F	6- -	4.700	4.4	2.26	+++	11.2
14	M	8- -	6.500	4.3	2.10	+++	10.0
15	F	5- 1	9.600	4.6	1.36	++++	12.0
16	M	6- 1	8.900	4.8	1.50	+++	11.1
17	M	6- 1	8.400	4.6	2.71	+++	10.9
18	F	8- 1	8.700	4.0	2.00	+++	11.2
19	F	1- 2	10.100	4.3	2.15	+++	11.4
20	F	1- 2	10.500	4.4	1.60	+++	11.3
21	M	10- 1	9.500	3.9	2.00	+++	10.8
22	M	2- 2	11.000	4.5	2.20	+++	10.0
23	F	-- 3	12.000	4.1	1.30	++++	13.0
	Averages			4.40	1.89		10.7

++ =moderately severe liver damage: marked fatty change, mostly limited to the peripheral zone of the lobules. (fig.1)

+++ =severe liver damage; universal distribution of fat inside the liver lobules. (fig.2)

++++ =Very severe liver damage: generalised fatty change together with some necrotic changes in the liver parenchyma and maybe some fibroblastic proliferation of the portal tracts.

centration in the corpuscles is twice that of whole blood, and gives the range of 5-8 mg% for whole blood and 4-5 mg% for plasma. It will be noted that our figures are in agreement with his. They are also in agreement with the figures obtained by Lyttle *et al*[5] for normal children which ranged between 2.9 mg% and 4.6 mg% for the plasma and are also very similar to the averages given for adults by Hamilton and Vanslyke[6] and by Woodruff and Mann[7], which for the plasma were 4.07 mg% and 4.23 mg% respectively.

II—Concerning Cases of Nutritional Oedema:

The blood amino acid nitrogen in these cases usually showed a much higher level than the normal. It varied from 8.7 mg% to 13.2 mg%, with an average of 10.8 mg%. Invariably all cases showed a severe degree of hypoproteinemia and hypoalbuminemia, the former varying from 3.5 gm% to 5.5 gm%, with an average of 4.4 gm% and the latter varied from 1.3 gm% to 2.7

Table III

It shows the body weight, total blood proteins, albumin fraction, liver condition and amino acid nitrogen content in whole blood in five cases, on admission and after clinical cure.

Sr. No	Time of Investigation	Weight kg.	Total blood proteins gm %	Albumin fraction gm %	Liver condition	amino acid nitrogen in whole blood mg %
1	On admission	12.500	4.1	1.31	++++	12.0
	after clinical cure	8.750	6.7	2.26	+	8.2
4	On admission	8.800	4.9	2.2	++	9.9
	after clinical cure	8.000	6.7	2.7	±Normal	6.8
15	On admission	9.600	4.6	1.3	+++++	12.0
	after clinical cure	8.500	6.4	2.9	+	9.0
17	On admission	8.400	4.6	2.7	+++	10.9
	after clinical cure	7.500	5.8	3.0	+	8.5
23	On admission	12.000	4.1	1.3	++++	13.0
	after clinical cure	10.200	6.5	2.6	+	9.2

+ = Liver shows very little fatty change or persisting fibroleastic proliferation of the portal tracts.

gm% with an average of 1.89 gm%. Liver puncture biopsy constantly revealed fatty change of considerable severity (Fig. 1 and 2).

On the whole, the rise in the amino acid nitrogen in the blood was noticed to be proportional to the amount of fatty liver damage, e.g., in Table II, case 1, 6, 9, 10, 11, and 15 which showed the most extensive fatty change, showed also the highest blood amino acid levels. On the other hand, though the blood albumin content was constantly low, yet its drop was not always proportional to the amount of liver damage. This could be possibly explained by the fact that the duration of the hypoalbuminemia is an important factor in the degree of fatty change which results.

Mann[8], had clearly demonstrated the key role of the liver in the deamination process. Ketamura[9], found that when the liver was directly damaged by phosphorous and similar poisons, there was an increased retension of amino-acids in the blood, Elman[10], working on normal and hypoproteinemic dogs found that there was a marked increase in the blood amino acids nitrogen in the latter cases as compared to the former, and that this increase was generally parallel to the duration and the degree of induced hypoproteinemia, and he gave evidence that this was probably caused by delayed rate of deamination.

Thus, the rise in the amino acid content in the cases studied can be explained by the fact that the hypoproteinaemia, from which they were all suffering, caused fatty liver damage, and this diminished the capacity of the liver for deamination. This is further confirmed by the fact that when the blood proteins were raised by high protein diet and plasma transfusion, the liver condition was greatly improved (Fig. 3) and the amino acid nitrogen content consequently returned to almost normal levels. (Table III).

Horjesi[11] and Dent and Walshe[12], stated that unless severe liver destruction exists, little information could be gained from the total amino acid nitrogen concentration in the blood. Thus the liver damage in severe nutritional edema must be extensive.

SUMMARY AND CONCLUSIONS

1. The amino acid nitrogen contents of the whole blood for normal Egyptian infants and children were estimated. Up to the present, figures for infants were not worked out, in Egypt or elsewhere.

2. In the normal cases, no variation was noticed with regard to sex, age or weight.

3. In cases of nutritional edema, blood amino acid nitrogen content, total blood proteins, albumin fraction and liver puncture biopsy were done. In these cases, a marked degree of hypoproteinemia, hypoalbuminemia and extensive fatty change of the liver, were always found together with a constant rise in the level of fasting blood amino acid nitrogen. It was also noticed that the rise in the amino acid nitrogen content runs parallel to the degree of fatty change in the liver.

4. Consequently, this high amino acid nitrogen content found in nutritional oedema could be taken as a measure for the severity of liver damage in this disease.

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MEDICAL ASPECTS OF READING FAILURES IN INTELLIGENT CHILDREN

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American educators are becoming increasingly concerned about children who fail in reading. It is significant that your organizations have become concerned also and are willing to help. An awareness of the dilemma should stimulate other branches of science, particularly psychology and medicine, to help determine and understand more fully the reasons for the great number of children and adults with reading disabilities. Also, the parents must realize the roles they play in this situation. It is through such understanding and multidiscipline cooperation that new ways of dealing with the problem will be developed and only by the scientific approach can this national plight be controlled.

The term, dyslexia, defines a syndrome which is characterized by an inability to learn to read properly even though the individual's intelligence is normal or superior. Dyslexia can not be considered as a simple reading disability. There are many ramifications extending into the physical, psychological and social fields as well. Abnormal factors which are associated with dyslexia are FUNCTIONAL, and correctible in approximately 85% of the cases, in contra-distinction to alexia, i.e. due to brain injury or lack of intelligence. In the entire syndrome one must investigate also the development of personality and emotional maturation and stability. In this investigation cognizance must be given to the hereditary traits and especially the environment in which the child lives. Occasionally, dyslexia is found in successive generations of the child's ancestors. This should not be interpreted as an inherited trait for most likely the characteristic environment has been experienced from one generation to the other. Before we ascribe dyslexia to genetic origin per se it would be necessary to eliminate all peripheral and functional disorders. There is nevertheless a possibility that heredity may occasionally contribute circumstances that predispose to dyslexia. Acceptance of the hereditary concept would be disastrous for then the parents, teachers and particularly the child would consider the condition hopeless and treatment would be doomed to failure.

Another source of bewilderment should be mentioned, with a forewarning. Caution should be a paramount consideration in the

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administration and interpretation of a psychological test. Accepting or implying that because children's I.Q.s have been reported as such without knowing the qualifications of the examiner is fraught with danger. Experience has shown that if the abilities of a child are rated too high or too low, teachers, parents and especially the child adopt compensatory methods with disastrous effects. This is emphasized when it is realized that the intelligence is not an innately acquired static quotient. It is a dynamic progression influenced by past experiences, motivations and the psychophysiologic needs and stimulations of the individual at any particular time. Actually, the psychological determination of the I.Q. is an estimate of the individual's potential. It is the differential, between the potential and the achievement of the dyslexiac child, in which we are interested today.

Reading is a complex achievement, and the more intelligent a person is and the more perceptual experience he has encountered, the more quickly he should learn from abstractions and symbols. The degree to which normal or abnormal functions influence the process of learning as a whole depends upon the individual's ability to maintain homeostasis in response to the psychophysiological stimuli that are imposed upon him. The degree of this homeostasic stability and adaptation depends on the degree of normality in all the diverse functions that are involved in the reading processes, including the central perceptual and conceptual processes as well as the entire peripheral ocular mechanism in all its complexity.

MEDICAL FACTORS

Due to our limited time, only brief mention can be made of some medical factors which we have found associated with dyslexia. First, let it be understood that there are many complexly interrelated determinates which make it hazardous to assign a single causative factor to reading disability. All possible factors are involved, such as physical, psychological and educational. However, one must be reminded that those factors do not act separately but as an integral in an environmental field to which in turn, the individual reacts as a whole.

It is singular that the ratio of failures in reading is approximately four times as many boys as girls. What are some of the factors which may influence such an uneven distribution of cases? This question can not be answered with finality but it is ripe for speculation. One could suspect an hormonal connection. Furthermore, apparently boys are more aggressive and rebellious than girls. Whether you believe that aggression is an inevitable mani-

festation of an universal "instinct," or whether aggression is one of the many defense mechanisms against frustration and insecurity, it still remains that there is such a phenomenon present regardless of the absence of an universally accepted explanation. The instinct of aggression appears to be much stronger in the males than in the females of the species. When children enter school, reading and learning can become a sublimation of the aggressive drive; and should this sublimation become thwarted, it is possible that dyslexia becomes a corollary.

Endocrines: As reviewed by Ivy and Krasno it is generally conceded that the endocrines, especially the thyroid gland, are influences in the maintenance of the intellectual functions and normal personality.

One of the most remarkable facts which experimental and clinical research determines in humans is that the optimum effects of the thyroid functions or medication upon mental growth occur before eleven or twelve years of age, and that administration of thyroid extract is almost futile after that age as far as mental growth is concerned. On the other hand, individuals who develop a hypothyroid condition subsequent to the full growth and maturation of their nervous systems do not manifest a true mental deficiency, although they may become lethargic, "dull" and physically sluggish, whereas, the hyperthyroid individual is irritable, jumpy and may be emotionally unstable. Adequate medication may change these states and make the hypothyroid patient more responsive and the hyperthyroid individual less reactive. Tentatively, it may be, however, that the quality of mentality and personality of these individuals in either case have not been changed. Normal mentality and integrated personality, depend a great deal on normal homeostasis, particularly the function of the nervous system. To that end the endocrines, especially the thyroid, are important in children. Subsequent to full maturity the personality and mentality of the individual are quantatively regulated by the effects of the endocrines upon the nervous system. In our study, 27% of the children had hypothyroidism, and 4% had hyperthyroidism, to a degree where therapeutic intervention was indicated. A few showed definite pituitary imbalances.

Reaction to Stimuli: Reflexes are suggestive of the status of the nerve reactions to stimuli. As ideas and learning are basically the reaction to perceptual experiences arising from sensations, both motor and sensory, abnormal reflexes influence the individuals ability to normally respond to sensations. Normally, according to his potential and ability to interpret his past perceptual

experiences the person is able to arrive at an understandable concept, not only of his environment but also of his own introspective responses, in harmony with his psychobiologic needs. Within the frame of references of general semantics a source of confusion is the lack of awareness of our abstractions and projective processes. As an example, use can be made of a stereoscope with a white card viewed by one eye, and a black area before the other eye which are superimposed by fusion. The resulting color then is interpreted as silvery gray. In identifying one level of abstraction from another the words *silvery gray* do not refer to the color on the card, as is so often naïvely assumed. Instead, it refers to the abstract determined by the individual's nervous system. In our cases 15% had sluggish reflexes, while 11% had exaggerated reflexes. Jerking of the head, twitching of face or other choreic symptoms were present in 6%.

Electroencephalogram: A preliminary analysis of the EEGs seems to indicate a tendency toward certain changes but precise opinions have not been formed. However, it should be pointed out that approximately 50% of the children had borderline or mildly abnormal EEG records. None could be considered severely abnormal. The most commonly observed borderline record was the unusually low build-up of voltage and slow waves during hyper-ventilation. Although this occasionally occurs in normal children, it occurred in approximately 30% of dyslexiac children. This is an observation which we shall pursue further. Some electrical alterations (always mild) occurred in the parietal lobe of the brain in approximately 20% of these children. This consisted of changes either from the normal rate or amplitude. However, once again care must be exercised in the interpretation of these data since parietal asymmetries can occur in normal children.

Bone Maturation studied by means of X-ray: Using as a criterion the carpal bone growth as standardized by Todd, 8% of the dyslexiac children show retardation in the chronological physical maturation. Some believe that reading failures are due to this slow maturational process. In a limited number of cases this may be the predisposing etiology, associated with other factors.

Blood: A comparison was made of the blood counts of 200 dyslexiac children with the standardized values established by Albritton. By correlating the number of circulating blood cells per cubic millimeter it was found that the erythrocytes were equal in the dyslexiac and standardized values. In the differential leucocyte count there was a variance. The number of circulating lymphocytes corresponded with the standardized values, but there was a

27% lowering of the normal differential for neutrophils. We are now carrying on a control study of this aberration to eliminate any possibility of an artefact, should there be one.

EMOTIONAL FACTORS

The incidence of enuresis in our patients has been 18%, i.e.—they gave a history of having had it, or it was still persistent. It is most unfortunate that we do not have time to consider the tremendous impact which the actions and reactions of the interpersonal relationships have between the dyslexiac child and his parents, siblings, teachers and playmates. The influence of a disturbance of these relationships must be a primary concern of any person involved with the care of a child with reading failures. When we consider that emotional factors are implicated as the outstanding cause of enuresis, and when we consider that emotional factors are related to the stability or instability of parental figures and home environment one must not overlook these phases in the investigation of any dyslexiac child whether or not he has enuresis. To clarify a point that might arise, it should be stated that enuresis is not felt to be a symptom of reading difficulty nor is reading difficulty secondary to enuresis. In many instances they are both symptoms of an emotional conflict which involves interpersonal relations with parents and siblings. The child may be reacting unconsciously to over-strictness, to much interference of inconsistent firmness in the family situation. It has been interesting to observe the correlation between the problem of enuresis and the neuropathic features of nail biting, thumb sucking, feeding difficulties and temper tantrums. Personality features are that the patient is inhibited, sensitive, timid, worrisome, fearful of the loss of parental affection and striving to please. Environmental factors of over-demanding, critical, perfectionistic parents might be responsible. A fear of loss of parent or parental love develops in the child when it fails to measure up to the parents expectations. That fear is often reflected in overcompensation to be a "good" child and please its parents while awake. However, when the child goes to sleep, confused feelings are released in night terrors, bad dreams and enuresis. Some have said that enuresis is an unconscious release of pent-up or repressed hostility of the day. One of our patients had an overbearing, teasing, proficient older brother who received recognition for his achievements to the embarrassment and frustration of our patient. There always seems to be a compensation, for it was necessary that these brothers sleep together. I will leave the remainder of this report to your imagi-

nation. In general, the problem of enuresis should be relieved of any feeling of shame, guilt or hopelessness that might have been developed by punishments, scolding or bribing. As enuresis is usually a corollary to other symptoms of personality disturbances, which are present almost without exception in dyslexiac children, it is well to look for excessive goals and standards, undue amount of criticism, or unfavorable competition. The home should be a place of security, serenity, encouragement and affection. Ideally, from the child's vantage point, the parents must personify all things that are good and wholesome.

AUDITORY AND SPEECH

Hearing is such an essential factor in language function it is important that a detailed examination be made. Acute otitis media is usually the cause for diminution of hearing in most cases. This may accompany an acute or chronic infection of the nasopharynx as evidenced by hyperplasia and inflammation of the tonsils, adenoids, turbinates or hypertrophied lymphatic nodules on the posterior pharyngeal wall. Furthermore, as evidence of the severity of the early children diseases which our patients had experienced, 14% gave a history of having had abscessed ears.

If a child cannot hear properly the influence upon spelling achievement is particularly noticeable, for apparently he misinterprets oral instruction and seems to become willfully heedless. Due to the hearing loss, the child may appear stubborn, indifferent, "dumb" and eventually becomes an extreme introvert the more he withdraws from social contacts. It is necessary that communications and directions, given by parents and teachers to this child, be heard and understood. By all means seat the child in the school room to the best advantage.

Whereas vocalization is the phase through which most of our ideas and instructions are expressed, and since it is so closely related to hearing, one must consider the physical development and flexibility of the vocal organs and the ability to coordinate and control them during the production of speech sounds. Nine percent of our series were late in learning to talk. Many children who are unstable emotionally will show a blocking when required to read either silently or orally. We have had cases where they would become so emotionally upset and frustrated their voice became tremulous, their face became pale and nervous twitching of the face was visible. It is quite evident that no one, however expert, could teach a child in that state of homeostasis

VISUAL FUNCTION

It is the customary concept that reading is simply seeing words, phrases and sentences. If it were as simple as that then the visual processes would be practically the predominant factor in dyslexia. When a discussion of dyslexia is begun with most people, they preface the conversation with "that must be due to eye trouble." It is most unfortunate that this concept is now being promoted. Within the last two months there have been a series of radio announcements on Chicago stations stating, "if your child has reading difficulties be sure to take him to an optometrist,"—perhaps implying that the eyes are the primary cause for reading failures. Such a campaign should be discouraged, but at least the optometrists have become interested and are doing something about it.

Now off on a tangent, unfortunately the same cannot be said about ophthalmologists and physicians in general. For twenty years our concern has been to interest physicians, psychologists, public and mental health programs, and other disciplines to help the educator—to little avail. However, in order to gain the full benefit of the multidiscipline approach, the policies and attitudes of the school administrators, teachers and particularly the parents must be tempered to the child, and to realize that the responsibility for having the child learn is not solely on the teacher's shoulders. This, by no means, relieves the teachers of their important roles in education.

Now let's get back. Only 19% of our cases need spectacles. Many pair of glasses were removed which had been prescribed empirically to aid the patient with his reading. Such a procedure should be frowned upon, when glasses are not necessary, for some of the children had a high degree of exophoria which was aggravated by the convex lens.

Fifteen years ago the number of investigations and publications dealing with the controversial question of dominance, eyedness, handedness and footedness were considerably more than at the present. In our experiences the conclusion is that these functions are not significantly related to reading ability.

Weak duction reserve, coincident with convergent insufficiency or accompany accomodative or convergent spasm, was present in many patients which caused undue fatigue.

Dyslexia cases were inferior in their ocular function to that of the "norms" where rate of reading, number of fixations, regressions and span of recognition were considered.

There are other erroneous ideas about the causes for reading difficulties. Among these are the concepts of strephosymbolia and

mirror vision, as shown in reading, writing and drawing, substitutions and reversals. These are apparently self imposed psychological processes, maybe accidental at first, but with definite significance when analyzed in relation to the aspirations and motives of the child. He may use this as a means of getting attention, or an escape, by having other people believe he has a rare malady, so, therefore, he is not supposed to learn to read. In our experience we have found no cases of typical mirror reading. We have had several cases who were using these mental gymnastics when we first saw them. One of our patients first began to write his name and also 3's, 5's and 7's backward. A presumed authority had spent two hours explaining to the Mother how the function of her son's right hemisphere of the brain had been transplanted to the left hemisphere, and the left hemisphere had been interchanged to the right. Naturally, the Mother was extremely apprehensive. Our concern was to find the reasons why the boy was using this excuse and technique for not learning in school. We did. He gained one year in reading within six months. Why not? He had an I.Q. 136. He also stopped his "monkey business".

Another boy had used this type of mental gymnastics in school for five years. Even on his first visit to the Institute he drew a picture of a cat standing on his head on a broom-stick. During the interview with the patient, in trying to determine his viewpoint and why he had drawn the picture thusly, his answer was: "I wanted to show the cat with his feet on the broom handle. Something happens to my brain that no one can explain so I don't know why the feet aren't on the broom handle." He really had his trouble. He also described seeing things upside down in past years, saying, "I would see spots before my eyes and these would be upside down." He cleared up also.

Now in brief, it would be erroneous to take the peripheral ocular mechanism habits as the standard and the visual acuity as the determinant of cerebral action or perceptual processes. It is also inconclusive to take mental processes as the sole factors influencing the modus operandi of peripheral ocular performance. Since the roles are probably interchangeable, it would be difficult to determine which acts as the originator and which the compensator. All available faculties plus the desire to achieve the universal concept are probably integrated in the processes of learning.

As a summary of the observations made in this discussion, it is pertinent to give as a resumé the following truism; after the major difficulties that prevent proper reading are corrected and hygiene of the body and mind as a whole is brought about, then and then

only may one feel that the first prerequisites have been fulfilled for specifically attacking reading difficulty. The final goal is to get the child to read for himself for pleasure.

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HOTTINGER, A.: Liver-Immaturity and Treatment of Kernicterus of the Premature Baby. (Indian Journal Pediatrics, 25:184, May, 1958).

There are different ways of showing that the liver of newborn normal children and even more premature children is functionally immature. This immaturity of the liver is the most important factor occasioning the kernicterus. The kernicterus-situation can be defined through the contents of bilirubin in the blood of over 20 mg./100 c.c. with a low percentage of so-called direct bilirubin (under 10-15%). Anoxemia-defects of the brain, of the liver, or other organs raise the danger of kernicterus.

There is no prophylaxis or therapy for the icterus of premature babies which is not caused by incompatibility. The only method is the exchange transfusion. It is not dangerous and can be performed even after the umbilicus has fallen off. In spite of the exchange transfusion a kernicterus-situation may occur a second time if bilirubin accumulated in the tissues is diffused into the blood. This requires a second exchange transfusion.

Indications for exchange transfusions: 1—small premature children, critical situation more than one day; 2—heavier premature children, critical situation more than three days: 3—symptoms of anoxemia, require a rapid therapy, at the latest on the second day of a critical situation.

AUTHOR'S SUMMARY

USE OF INTRA-MUSCULAR IRON FOR IRON DEFICIENCY ANEMIAS OF PREMATURE INFANTS

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Several months ago, the author noted a disturbing phenomenon while on the premature nursery service of a large county hospital. Several of the premature infants displayed marked abdominal distention, some to the point of embarrassing respirations. Occasional cyanosis was noted in those infants with marked distention.

Careful examination of these infants showed no enteric disease or other apparent illness other than a typical iron deficiency anemia. All of these infants were taking a commercial preparation of ferrous sulfate solution by mouth. These infants, along with most of the prematures, were also taking daily doses of a commercial vitamin drop preparation, but none of the infants taking vitamin drops alone displayed abdominal distention.

The ferrous sulfate drops were discontinued on all premature infants taking them, and the abdominal distention promptly ceased. Re-administration of the drops appeared to cause a prompt recurrence of distention, and the medication was discontinued.

The problem now facing the medical staff was how to deal with the anemia which several of these infants displayed, with packed cell volumes or hematocrits ranging downward to 16% and hemoglobin values to 5 and 6 grams per 100 ml of blood. Use of whole blood transfusions was considered but discarded in view of the technical troubles, and the dangers inherent to transfusions. It is also largely believed that whole blood transfusions may depress erythropoiesis. Use of intravenous saccharated iron preparations was considered, for this treatment has proven effective in iron-deficiency anemias, but this technic is also troublesome, and not without toxicity.[1] Use of other oral preparations of iron was considered. However, the immaturity of the premature's gastro-intestinal tract is well known, and absorption of iron is a complex affair requiring, at least, the active cooperation of the intestinal tract.[2,3] Use of a relatively new iron-dextran complex, Imferon, ®* for intra-muscular injection was considered. Our attention was directed to a paper by Wallerstein who described the use of this material in anemic infants in a neighboring city.[4] Although the total number of infants treated in this report was small, the absence

of toxicity and good response of the erythropoietic systems seemed encouraging, and a review of the literature indicated that Imferon® was well tolerated, safe, and effective. Further reports by Wellerstein and his co-workers have strengthened this impression.[5]

METHODS AND MATERIALS

Six infants were selected for a trial course. Those selected all suffered from the typical iron-deficiency anemia of prematurity, and all had displayed abdominal distention, presumably from the oral ferrous sulfate. Since the hospital was seriously handicapped by a shortage of technicians and house staff, it was decided to keep the laboratory work to a minimum. Our purpose was twofold: to determine (1) if the drug was safe and (2), if it was effective. Wallerstein's report had indicated a maximum reticulocyte response on the fifth day after administration of the drug. In our series, therefore, we secured reticulocyte counts on the first and fifth days. Packed cell volumes and hemoglobins were obtained on the first day, and weekly thereafter. The infants were not selected by age or weight, but the weight ranged from three to five pounds. There was no control group as such, but our results were compared with the untreated infants.

Nursery personnel were instructed to watch the treated infants closely for toxic or unusual signs. The injections were given by the house staff or by the nurse in charge under the supervision of the resident. Actual choice of a site for the intramuscular injection required some thought, as premature infants are deficient in muscle mass. Final choice was either the gluteal or anterior thigh area, depending on which seemed to be larger in mass. The "Z-track" method of injection was used, following the recommendation of the manufacturer. This method minimizes seepage of the drug from the injection tract, and keeps staining to a minimum. Although precise formulas[6] have been devised for determining the total dosage of Imferon® required, this method was not used by us except as a rough check of total dosage. Following the dosages employed by others, we gave 0.5 cc of the drug—representing 25 mgm of elemental iron—at weekly intervals, from one to four injections.[7] Use of larger doses at one injection presented the problem of the material oozing out of the injection tract with subsequent loss of drug and staining of skin and subcutaneous tissues. The larger doses were given to the larger infants or those with the more profound anemia.

RESULTS

All six infants showed an increase in reticulocyte counts when checked on the fifth day after the initial intra-muscular injection of the drug. In a follow-up period of two months, the packed cell volumes either increased or remained constant—which represents absolute increase due to growth of the infant. The hemoglobin values increased in all six infants.

No signs of toxicity, and particularly, no evidence of hemosiderosis was noted. No abdominal distention was seen. No local reaction other than transient staining of the skin was noted, and this was minimal.

Unfortunately, and for many reasons, long term follow-ups were not available on these patients. Word of mouth reports had it that the infants continued to "do well" after discharge to their homes.

DISCUSSION

A brief review of iron metabolism is necessary for a meaningful discussion of our results. Infants have no practical route for the physiologic excretion of iron, once absorbed.[2,3] The newborn infant normally has an adequate amount of red blood cells with a suitable hemoglobin concentration. Growth of full term infants is rapid, with a doubling of birth weight by five months considered normal. If red blood cell production should not keep pace with this somatic growth, an anemia will result, and commonly does. From 50 to 90% of the hemoglobin present at birth in a full term infant is of the fetal type—so-called hemoglobin F. A higher percent of hemoglobin in prematures will be of this type. Production of the adult type hemoglobin with new red blood cell production may not begin until the third month after birth. Most diets supplied premature and full term infants are markedly deficient in iron, and hemoglobin production may suffer accordingly. However, "physiologic" destruction of infants' red blood cells leaves the iron within the body for re-synthesis into more hemoglobin. Milk is notoriously low in iron, yet forms the chief dietary item in the first trimester of extra-uterine life, and is often the chief item during the first year. Adults will assimilate about ten per cent of iron present in ingested food, and babies may absorb somewhat more.[3] How-

* Imferon ® is the registered trademark of Lakeside Laboratories, Milwaukee, Wis., for their brand of iron-dextran complex for intra-muscular use. See New and Nonofficial Drugs *J. A. M. A.* March 22, 1958.

ever, the status of assismilation of iron in the premature is unknown, and it is likely that it is less than in the full term infant—possibly due to the notorious sensitivity or intolerance of the premature's gut. Available iron present in ingested food is not mechanically absorbed from the gut, but actually requires a metabolic or enzymatic "absorption" or transfer. This is often called the "mucosal block" because acceptance of iron to the body seems to be controlled here, it being remembered that there is no excretory route of any importance, and once iron is absorbed it is in the body "for keeps". Once across the "mucosal block", iron may be stored as ferritin in the liver or spleen, or as hemosiderin in the liver, spleen, or bone marrow. Or it may be manufactured into myoglobin, cytochromes, or hemoglobin. With the premature infant deficient in muscle mass, it is now easy to see how as the muscles grow, myoglobin formation takes much of the available body supply of iron—leaving less for hemoglobin formation.

From the foregoing facts we may make a few conclusions. Iron deficiency anemia, the so-called "anemia of prematurity" will result unless exogenous iron in adequate amounts is presented in the diet or given parenterally. As indicated, normal dietary sources of iron are inadequate, and oral iron preparations may not be absorbed, or be highly irritating. We may predicate that the "mucosal block" of the premature infant does not function at the full level of the full term baby. This predicated hypofunction may be no more than intolerance of the intestinal mucosa to the iron salts, but the end result is the same—inadequate absorption. Premature infants with typical iron deficiency anemias who are intolerant or oral iron, or do not respond to same with increased erythropoiesis might well be considered for a course of parenteral iron. Once the trial is begun, the reticulocyte count should increase, and the hemoglobin show a definite increase within three weeks of starting therapy, or other types of disorder should be considered.[5] In a group of sixty-six premature infants, Hammond and Murphy found that these babies were able to utilize injectable iron by the second month of life, and no untoward or toxic signs appeared.[7]

It would also appear from the reports of others that the beneficial results of Imferon® given early may persist through the first year—when the incidence of iron deficiency anemia is high under untreated conditions. Some workers have felt that a premature infant may well be given enough iron intramuscularly during his hospital stay to suffice or at least assist him through

the first year. This application may find use in anemic infants and children of ignorant or careless parents, as it definitely answers the oft-asked question, "Has the iron been given?"[6] It is well to stress here, with other workers, the importance of meticulous umbilical cord stripping at the time of birth to assure the infant a temporary over-supply of blood. This will assure more iron stores *in the body* for later re-synthesis at the period of need.[3]

SUMMARY AND CONCLUSIONS

1. Six premature infants having the typical iron deficiency anemia of prematurity appeared to have marked gastro-intestinal distress from the oral administration of ferrous sulfate drops.

2. An iron-dextran solution, Imferon®, for intra-muscular injection was given a trial in place of the oral medication.

3. All infants showed a good response, with increased reticulocyte counts, and absolute increases in hemoglobin and hematocrit values.

4. There were no signs of toxicity from the intra-muscular iron injections. Occasional transient staining of the skin at the injection site was noted.

5. Brief comments are made on the metabolism of iron, and its application to our results was discussed.

6. Intramuscular iron-dextran complex appears to offer a safe and effective method of treatment for the classic iron deficiency anemia of prematurity.

The author acknowledges with thanks the invaluable assistance of the nursing and laboratory staffs in this study.

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Fayetteville, N. Y.

Clinical Conference

ST. LUKE'S HOSPITAL, NEW YORK

May 12, 1959

J. FREDERICK EAGLE, JR., M.D.,

Director of Pediatrics, presiding

CONGENITAL HEART DISEASE

INTERVENTRICULAR SEPTAL DEFECT

DR. WALTER G. WEEKS, Intern on Pediatrics: M. L., an eighteen month old female, was first admitted to St. Luke's Hospital at the age of 2½ months in December, 1957, with the presumptive diagnosis of congenital heart disease. She had a poor appetite, had failed to gain weight, and had occasional duskiness on crying since birth. On examination at home, her physician had found enlargement of her heart and a murmur. For a few days before admission she had an elevated temperature and had been coughing. Physical examination revealed a small, thin, moderately active baby weighing 8 lb. 3 oz., approximately 1½ lbs. over her birth weight (6 lb. 13 oz.). A Grade IV harsh systolic murmur was heard over the precordium and radiated to the back. There was also a palpable thrill. Both femoral pulses were easily felt. The liver was down 2 cm. below the right costal margin. There were no other significant findings.

X-ray studies revealed minimal cardiac enlargement with bilaterally increased pulmonary markings. An electrocardiogram revealed right ventricular hypertrophy. It was felt that she had congenital heart disease complicated by left-sided failure and bronchopneumonia. Therapy consisted of digoxin and antibiotics to which she responded fairly well. On discharge it was felt that she had an interventricular septal defect. She was maintained on digoxin, with prophylactic antibiotics and has been on these medications until her present admission. She began to gain weight after discharge.

Her second admission was in April, 1958, at the age of five months for bronchopneumonia. She was treated with therapeutic doses of penicillin and achromycin and responded satisfactorily. In the ensuing months she did extremely well except for frequent upper respiratory infections, gaining in height and weight at a rate which was only a little below the norm for her age. Motor and intellectual progress was entirely normal. She had no cyanosis. However, her

heart continued to enlarge. Electrocardiograms persistently revealed right ventricular hypertrophy, and physical examination continued to reveal the murmur and thrill. As she grew, the second pulmonary sound became loud and snapping.

Cardiac catheterization was carried out on her third admission in January, 1959, at the age of 14 months when she weighed 17 pounds. This study proved the presence of a large interventricular septal defect and a marked degree of pulmonary hypertension.

At the age of 18 months, weighing 20 lbs., she was admitted for corrective surgery by the open heart technique. This was carried out successfully with the use of a heart-lung machine. Her postoperative course was most gratifying.

DR. ADELE D. HOFMANN, Ass't. Attending Pediatrician: As her pediatrician I have followed this child at monthly intervals since she was four weeks of age. When she first came to us she had a cardiac defect which was incapacitating. She coughed continually. It was felt that she was in cardiac failure with a bronchopneumonia. Also, she was a feeding problem taking only two ounces of formula at a time. For the first few months of her life she had to be fed every two to three hours around the clock. Her weight gain was slow until she was four months of age. I was very worried about her and wondered whether she would ever make any progress. We have all seen young infants with chronic heart disease who fail to thrive and not infrequently expire in their early months. But many of these children gradually balance their shunts, equalize the pressures in the right and left side of the heart and temporarily, at least, begin to do very well. At the age of four months she began to eat better and gain weight. She stopped coughing, although she had more respiratory infections than are expected in the average child. We believe that prophylactic antibiotics prevented more serious illness and feel that such protection is important since serious infection might have precipitated cardiac failure.

The persistence of right ventricular hypertrophy kept us aware that this child still had a major problem although she was growing and developing satisfactorily. We knew from practically the day that she was first seen that cardiac surgery would be necessary but surgery on a seven or eight pound infant is rarely carried out successfully, particularly on one in borderline failure. We hoped to keep her well and permit her to develop and gain weight until she reached an age when catheterization and surgery are technically easier to perform. Fortunately she grew as we hoped.

In December, 1958, it was felt that she was of a size where catheterization could be carried out quite easily. We wanted to confirm our clinical diagnosis, but of equal importance was a determination of the pulmonary artery pressure. If this was elevated we would try to correct the defect soon. If it was not elevated to a level that alarmed us we would wait another year or more. Catheterization did show that there was significant elevation of pressure on the right side of the heart and we felt that surgery should be carried out in the near future. The delay of three months was an arbitrary one, primarily to do the surgery at a period in the year when she would have a fairly good chance of being infection free.

In conclusion, I would like to summarize the responsibility of the pediatrician for the patient with congenital heart disease with a left to right shunt. First, he must vigorously treat the early phase of cardiac failure realizing that the child will probably not withstand surgery in the first few months of life. However, there is a good chance the child will compensate and begin to do well in three or four months. Second, he must be aware that the outward appearance may lull a physician into a false sense of security. Persistant cardiac enlargement should motivate early investigation well before the patient enters into a downhill phase which will inevitably occur when pulmonary hypertension develops at any time from two years of age on. Third, the physician must be aware that the risk and difficulty in performing both catheterization and surgery are increased in the small infant. Surgeons are reluctant to operate on anybody weighing less than 20 pounds, although they will attempt a procedure if it appears to offer the only chance of survival. The pediatrician follows the child closely over a longer period of time than any other physician involved and it is his responsibility to be the constant mediator between the patient and the cardiac-surgery team.

DR. A. L. LOOMIS BELL, JR., Associate Cardiologist: There were several very interesting and, I think, pertinent, aspects of this case that I would like to touch on briefly. In the first place, whenever a child goes into congestive heart failure within the first few months of life there is a serious cardiac defect. If the congestive failure is refractory to adequate medical management, definitive diagnostic procedures are indicated at once, since in this event corrective surgery, even though at great risk, offers the only hope of survival. Fortunately, this child responded well to the excellent medical regimen instituted by Dr. Hofmann and definitive diagnostic procedures could be deferred. We felt that this child had a particular type

of heart failure, namely high output, left ventricular failure, a type wherein the left ventricle is pumping a great deal more blood than the right.

DR. EAGLE: What was your evidence for high output failure?

DR. BELL: The evidence for high output left ventricular failure was fever, rapid respirations, pulmonary congestion, a large heart, and a large pulsating liver, plus the fact that the murmur suggested a ventricular septal defect which is a common cause of high output left ventricular failure.

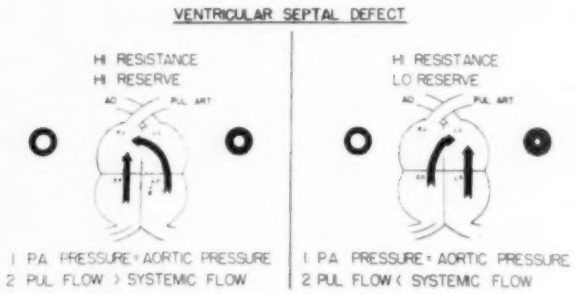

FIG. 1

There is some reason to feel that if the defect is large enough there is a perpetual state of pulmonary edema. You all probably know from the work of Dr. Barry Wood that pulmonary edema fluid is an ideal culture medium for any bacterium and that these children are prone to repeated pulmonary infections. Very often they are admitted with pneumonia or bronchopneumonia as the presumptive diagnosis, and while pneumonia may be present, more often it is associated with heart failure. The heart failure is difficult to demonstrate. The classical manifestation of rales, and peripheral edema are usually absent. Usually they wheeze, suggesting asthma associated with varying degrees of consolidation. Whether the heart failure is primarily left or right, in general we see an enlarged liver, but I believe, and you pediatricians know more about this than I do, the fact that the liver pulsates is a better sign of failure than the difficult job of deciding whether it is enlarged or not. We all know that the livers are almost always palpable in these small infants.

Figure I represents a diagram of what we believe takes place in large ventricular septal defects after birth. When the ventricular septal defect is large enough, anatomically defined as a size at least as large as the aorta, there is a common pressure presented to the

aorta and through the defect to the right ventricle and pulmonary artery. Blood will flow toward the least resistance and, if pulmonary artery resistance did not equal or nearly equal aortic resistance, virtually all the blood would flow from left ventricle to right ventricle to pulmonary artery. This, of course, would be untenable for life. Heart failure occurs when this shunt is excessive.

Thus, heart failure before a year of life, represents primarily failure of the pulmonary resistance to equal or nearly equal the resistance in the systemic circulation. This allows a tremendous shunt from left to right ventricle and into the pulmonary circulation back to left atrium, so there is a tremendous overload on the left side of the heart.

However, with age, pulmonary resistance increases. Early in life, the resistance of the pulmonary circulation is of the so-called high reserve type.[1] There is medial hypertrophy of the muscular pulmonary arteries with increased vasomotor tone, a reversible pathological change. In the progression from the left to the right side of Figure I, (I am not sure how many months or years this takes, perhaps as early as the age of two years) the following sequence of events takes place. In addition to muscular hypertrophy, pathological changes in small pulmonary arteries develop which are characterized by occlusive fibrous lesions associated with dilated smaller arteries and arterioles. When disseminated these occlusive lesions play the major role in determining pulmonary resistance which becomes very high and fixed. When the pulmonary artery resistance exceeds the systemic resistance then the shunt of blood through the defect will reverse, and the patient becomes cyanotic. Pulmonary flow is then less than systemic flow and, of course, the pulmonary and aortic pressures remain identical. If you wait for cyanosis to occur irreversible changes have developed and it is usually too late to do corrective surgery. If the ventricular septal defect is closed at this late stage, the patients do poorly and rarely survive surgery. The solution, of course, is to operate on these patients before this late stage of fixed resistance develops. At St. Luke's we have seen three children in the last two years who have passed to this irreversible stage; one at age four, one at age three, and one at age seven. How much earlier it can occur I don't know but I have talked with others who have seen it in two year old children.

Clinically, infants with large ventricular septal defects frequently are first seen in heart failure, but as the pulmonary artery resistance develops to nearly equal systemic resistance the shunt is reduced.

The work load on the left ventricle is thereby reduced and they then seem to do very well; they eat, they gain weight, they are not cyanosed, and parents and doctors alike are very frequently lulled into a sense of security that the child has a minor defect and there is no reason to pursue diagnostic studies for probable surgery. But if there are signs of pulmonary hypertension, such as right ventricular hypertrophy on the electrocardiogram and a loud pulmonic second sound, these children should be studied at an early age before the irreversible changes develop.

These are the variables that we were weighing in following this patient. We had to decide when to do diagnostic studies and when to operate. I do not think that any heart surgery should be undertaken electively if the child is under twenty pounds. If on the other hand, it becomes evident that the child is not going to live long enough to reach a weight of twenty pounds, an attempt should be made to obtain a precise diagnosis and perform surgery prior to that time. I think this is a very defensible point of view. But if the child, in response to good medical management, is doing well one delays catheterization or definitive studies. How long one can delay I do not know, but I believe diagnostic studies should be performed with surgery in mind sometime between the ages of about 1½ to 3 years if there are signs of pulmonary hypertension.

We did the diagnostic studies on this patient at the age of eighteen months. Figure 11 is a diagram of the catheterization data. If we look at the blood oxygen contents which are shown in the boxes, the superior and inferior cavae average about 8.2 cc. per litre. As soon as we get into the ventricle there is a sharp increase in the oxygen content which is sustained in the pulmonary artery. This means that there is an admixture of arterialized blood at the ventricular level. The aorta blood was essentially saturated and the calculated shunt was almost exclusively from the left to the right and amounted to about one-half of the systemic blood flow.

As far as pressures are concerned, the pressure in the right ventricle, 79/5, mg. Hg. is about three times normal. The systolic pressure is about the same as the pressure recorded in the femoral artery, and we assume that this latter is a reflection of the systolic pressure in the left ventricle. So we can say that there are essentially identical pressures in right and left ventricles and that the ventricular defect is large. If there is no protective degree of pulmonic stenosis this same pressure should present in the pulmonary artery and should therefore be a stimulus to the early appearance of irreversible changes mentioned earlier. However, when we measured

the pulmonary artery pressure we found a significant gradient of 40 mm. across the pulmonary valve. Ordinarily we would make an unqualified statement that there was a significant degree of infundibular stenosis which was protecting the pulmonary vasculature from the high ventricular pressure. However, in this case, we had a technically poor tracing and we were not certain that the pulmonary artery pressure was really this low. We actually managed the case as if the pressure in the pulmonary artery was identical with that in the right ventricle. We had reason to be sure this was proper later on.

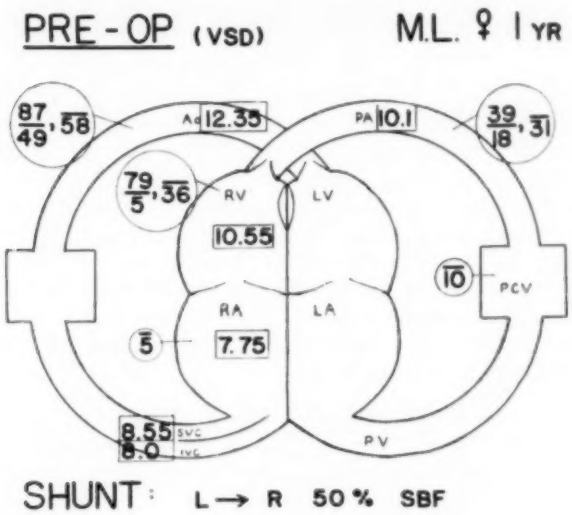

FIG. 2

The catheter studies provide physiologic evidence for admixture of blood at the ventricular level and a common pressure between the two ventricles. We have had identical catheterization findings in children with irreparable hearts, truncus arteriosus and one with atresia of the mitral valve, small left ventricle and large right ventricle with both aorta and pulmonary artery emerging from this chamber. Such a case would be a nightmare on the operating table. Therefore, it is prudent in a case like this to identify the roots of the great vessels and the chambers of the heart by angiocardiography and see that the anomaly is surgically correctable.

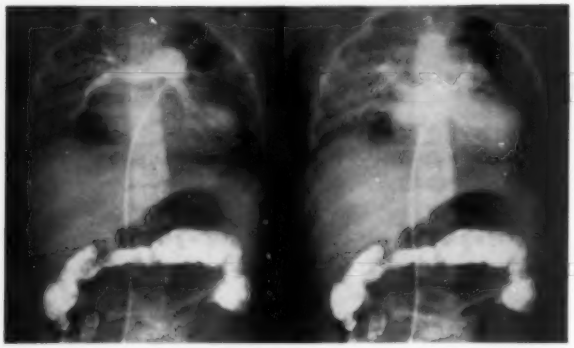

FIG. 3

Figure III shows representative angiocardiograms. The catheter is seen coming up from the femoral vein with the tip in the pulmonary artery. The film on the left is early in the sequence and shows a nice pulmonary artery, separate from the aorta. The film on the right, later in the sequence, shows dye in the aorta, the left ventricle, the left atrium, and dye can be seen filling the right ventricle through the high septal defect. There is no question that the pulmonary artery has become reopacified from the left side of the heart. The selective angiocardiogram proves the presence of normal aorta and pulmonary artery roots and locates a high ventricular septal defect with left to right shunt of the dye.

Figure IV is a pressure tracing taken in the operating room, before and after closure of the defect. Both the tracings in pulmonary artery and right ventricle have a common zero and common sensitivity. The pulmonary artery systolic pressure is only slightly lower than the right ventricular pressure indicating that the degree of pulmonic stenosis is slight and pulmonary artery and aorta pressures are essentially the same. We would have been misled if we had assumed a significant and therefore protective degree of pulmonary stenosis. The ventricular pressure approached 75 mm. pre-operatively. After repair of the defect, the systolic pressure dropped from 75 to 35 mm. and the small pressure gradient between ventricle and pulmonary artery during systole was abolished. This indicates that any pulmonic stenosis was relative to the high flow when the shunt was open and is now abolished. These tracings reflect a wonderful pressure response to closure of the defect, normalization of the pressures in the right ventricle, and as you can see, a good high

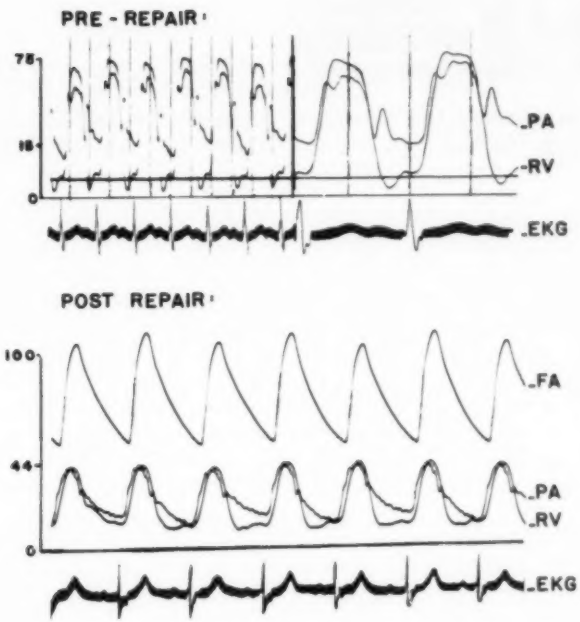

FIG. 4

pressure on the left side of the heart as reflected in this femoral artery pressure of over 100 mm. Histologic sections of a lung biopsy taken at operation revealed the entirely reversible early changes of medial hypertrophy of the small pulmonary arteries. No occlusive lesions were seen.

DR. HUGH FITZPATRICK, Associate Attending Surgeon: This patient had a high interventricular septal defect that was about 1½ cm. in diameter, certainly as large as her aorta. She was on the heart-lung machine for 27 minutes and withstood the operation very well. We ran a flow of 625 cc. a minute, which was estimated to be 60% of her resting output.

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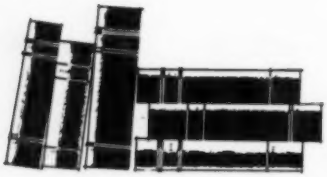

. . . Books

Edited by

MICHAEL A. BRESCIA, M.D.

INBORN ERRORS OF METABOLISM, by David Yi-Yung Hsia, M.D. Cloth. Illustrated. Pp. 358. Price $9.50. The Year Book Publishers, Inc., Chicago, Ill., 1959.

Dr. Hsia has written an invaluable book which should be read by every pediatrician. He has systematized many important clinical entities the importance of which are of recent vintage and in so doing he has given the proper orientation and perspective to many erstwhile vague clinical syndromes. The book is considered under five important parts. The first part deals with disturbances in molecular structure under which he discusses sickle cell anemia, other abnormal hemoglobins and other structural disturbances such as thalassemia, Pelger-Huet anomaly of the leukocytes, etc. Part two deals with the disturbances in molecular synthesis under which the author includes deficiencies of the plasma protein fractions such as congenital agammaglobulinemia, ceruloplasmin deficiency (Wilson's Disease) and congenital afibrinogenemia as well as deficiencies of the clotting factors. The third part deals with disturbances of molecular function under which the author includes disturbances in amino acid, carbohydrate, endocrine and pigment metabolism. The fourth part deals with disturbances in renal transport mechanisms and the fifth part considers disturbances in which the etiology is unknown under which heading the author considers among other matters, disturbances in lipid metabolism and the muscular dystrophies.

The appendix to this volume consisting of some 55 pages contains an outline of the many laboratory procedures which are necessary to help diagnose the many conditions discussed in the text. This part of the book will be of great value to many laboratories in which many of these tests are not routinely performed.

M. A. B.

FRANCONI, G. AND WALLGREN, A. *"Lehrbuch Der Paediatrie"*. Cloth, Pa. 1007, Illustrated, Price . . . . Basel, Stuttgart: Benno Schwab & Co., 1958.

The need for a fifth edition of this standard work speaks well of its popularity in Europe. It has been translated into many foreign

languages and obtained a place in the international literature. This well-arranged and comprehensive textbook covers essentially all aspects of modern pediatrics. A number of new authors have joined the ranks of the 23 contributors, some of them men of international distinction. They have brought the material up to date and included some late advances of scientific research in the process of covering the fundamentals of pediatric practice. Emphasis has been placed on normal and pathological aspects of physical and emotional growth and development. The international character of the work allows the student to become familiar with differing viewpoints of authors from various countries. The two renowned editors have again attempted to coordinate individual sections by eliminating repetitions and adding some important facets.

The book contains a wealth of excellent illustrations, tables, diagrams and color photographs. The latest edition of this outstanding textbook will be a very valuable instrument for the student and general practitioner and will also provide stimulating reading for the specialist. M. W

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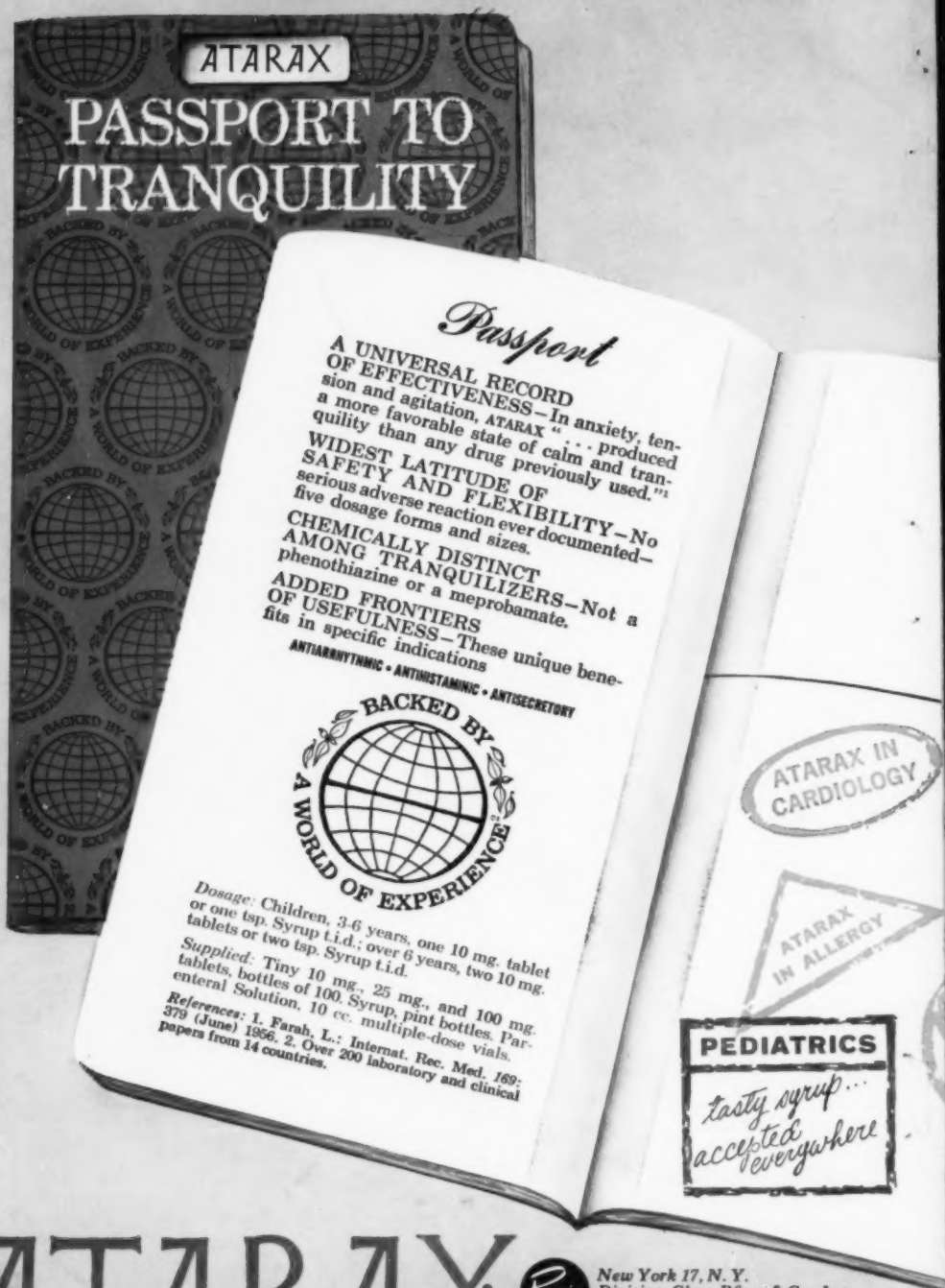
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